Original Article

Insights Into Emerging Natural Products For Treating Alzheimer's Disease

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Abstract

Chronic neurodegeneration is the underlying cause of the cognitive decline and dementia in the elderly, including Alzheimer's disease (AD). As a result, the patient's memory progressively declines. The growth of senile plaques and neurofibrillary tangles (NFT'S) are important diagnostic markers. The primary causes of Alzheimer's disease are a lack of Acetylcholine (A Ch) availability in the cerebral region due to metabolism by the enzyme Acetylcholine esterase and neural death. Additional stress-reducing methods to treat Alzheimers include incorporating Nutraceuticals into a person's diet, Aromatherapy, and making changes to their daily schedule, as well as regular yoga practice. These methods have been shown by researchers to be most effective in releasing stress. Because of its wide availability, cheap cost, high patient compliance, simplicity of formulation, and lack of harmful side effects, herbal medicine is now the greatest option for treating AD. Herbal medicines may be developed using cutting-edge methods. AD, its pathophysiology, the various stages of the disorder, various selective therapeutic targets for AD, available Anti-AD herbal drugs, herbs with essential oils, volatile oils and the source and cultivation of the herbs are all covered in this review.

Keywords: Alzheimer's disease, Neurodegenerative disorder, Plants, Herbal, Extract, Phytoconstituents

INTRODUCTION:

Alzheimer's disease (AD) is a degenerative brain illness that causes memory loss, personality changes, and other behavioral problems. APP and the presenilin gene, which encodes for proteolytic enzymes, have been shown to be duplicative or mutant in AD, resulting in high levels of neurofibrillary tangles and β-amyloid. AD biomarkers include brain neurodegeneration and β-amyloid accumulation in the brain. The combination of environmental and genetic variables, as well as aging, causes neurodegenerative illnesses. AD may proceed for years without showing any clinical signs, eventually leading to cognitive deterioration. Normal brain activities are disrupted in the early stages of AD, which results in a lack of ability to build new memories and a fast loss of previously acquired knowledge. Plaques develop, followed by inflammation, loss of cholinergic function, and stress, all of which are symptoms of the disease. Inflammation of the central nervous system (CNS) brought on by changes in the microglia raises the risk of cognitive decline and AD. When the body is in a healthy condition, antioxidant enzymes are able to counteract oxidative stress, but with AD, the brain's antioxidant enzymes become dysfunctional. The perirhinal area, the hippocampus complex, and finally the temporal lobes with the basal forebrain are all affected by AD pathology. Patients' well-being is harmed by AD, which is mostly a mental illness. Alzheimer's disease patients' quality of life may be assessed by changes in their behavior, both good and negative. Apolipoprotein E_4 allele, aging, education, gender, and apolipoprotein E_4 allele are all risk factors for AD. AD and dementia are linked to cardiovascular disease, diabetes, and smoking [1].

AD risk was reduced significantly by screening and managing cardiovascular diseases such as stroke, blood pressure, and other problems, contrary to the earlier belief that cardiovascular risks, trauma, smoking, and family history of alcohol and non-steroidal anti-inflammatory drugs (NSAIDs) have no significant impact on AD. These factors are not related to the development of AD. Cognitive activities like reading, watching television, and playing video games all lower the chance of developing Alzheimer's and other forms of dementia. Cognitive impairment may be induced by the use of non-psychotropic drugs like digoxin and antihistamines that interfere with neurotransmitter activity. The number of persons with AD and other forms of dementia is on the rise across the world as a result of variables such as population expansion, aging, and technological advancement. Dementia now affects 40–50 million individuals worldwide, up from the original estimate of 20 million in 1990 [2].

AD and dementia account for 2.5% of all fatalities worldwide, with neurological illnesses accounting for 12% of all deaths. Between 1990 and 2016, the mortality rate from dementia rose by 148%, making it the fifth leading cause of death. AD and other kinds of dementia would affect one in every 85 people by the year 2050, according to current estimates of the 7.7 million new cases diagnosed each year. AD is more common in the elderly, with a prevalence rate of 25 to 50 percent greater than in young individuals. The rising prevalence of AD and other metabolic illnesses may be mitigated by early

identification and adequate treatment. AD causes more than three-quarters of all cases of dementia in the elderly population, hence age is a significant risk factor. AD accounts for around 30 percent of all instances that begin before age 65, and the early beginning before that age is very rarer, with an incidence of fewer than 1 in 4000. Research into the pathogenesis of AD and the risk factors linked with AD has increased as the incidence of AD has increased. Inherited risk factors including gender, age, and family history pale in comparison to the impact that lifestyle and certain medical problems that can be managed may have on the development of AD [3].

Hyperphosphorylated tau protein (neurofibrillary tangle formation), which is a major hallmark of AD, as well as β-amyloid deposition in the grey matter of the brain contribute to cognitive impairment and eventually lead to Alzheimer's disease in the brain. The buildup of amyloid triggers an immune cell infiltration, which then causes inflammation to occur. Neuronal death and cognitive impairment are both consequences of this disruption of cell communication. Accumulation of beta-amyloid plaques in the brains of AD patients is associated with the proteases butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and β-amyloid secretase-1 (BACE-1). The apolipoprotein E (APOE) gene (60–80 percent) is one of the most important hereditary risk factors. Presenilins (PSEN I and PSEN II) as well as APP are implicated in the early start of Alzheimer's disease, and the APOE gene has been identified as the most significant causal gene. The β-amyloid theory of AD is based on the finding that excessive levels of β-amyloid are caused by overexpression of the APOE gene. Electrochemical reactions in the mitochondria produce hydrogen peroxide, which damages cells and is linked to mitochondrial dysfunction. β-amyloid and tau protein deposition compensates for and controls this damage in the early stages of the illness. Antioxidant activity is reduced in AD as the illness advances, resulting in the formation of reactive species that produce severe oxidative stress. When there is a buildup of tau protein and β-amyloid in the brain, acetylcholinesterase activity decreases. Multiple features of AD pathology may be mitigated by inhibiting leukotriene signaling in brain cells. This, in turn, reduces inflammation and degeneration in the brain. In order to accurately diagnose AD, a postmortem brain scan is necessary. However, the methods now used to measure blood and CSF levels of β-amyloid and tau proteins are unreliable, and new ones must be developed [4].

AD development may be slowed by the use of appropriate treatment and preventative measures. The prevalence of AD may be reduced by modifying one's lifestyle and engaging in regular physical exercise. Cost-effective initiatives should be launched to improve the treatment and prevention of Alzheimer's disease and other forms of dementia. Diagnosis of AD in its early stages relies on measurements of amyloid, tau, and genetic susceptibility, as well as changes in blood vessels and hearing loss. AD may now be diagnosed using MRI and PET scans, which are more accurate. There is no effective therapy for AD at present time due to the disorder's complexity. As a result of their negative effects, these medications are used to halt the advancement of the illness. Various herbs and preparations of these plants have traditionally been used to boost memory and cognitive functions. Secondary metabolites found in plants have the potential to treat AD. Using the findings of this review study, we will be able to design natural-source medications that are both successful and cost-efficient in the treatment of AD [5].

Dementia and AD may be alleviated by medicinal plant secondary metabolites. It is also straightforward to produce anti-AD drugs from natural sources since natural compounds are diverse in structure and function. There is medicinal efficacy, AChE inhibitory action, redox metal chelation, antioxidative and antiinflammatory capability, and aggregation inhibition and hyperphosphorylation of tau proteins in herbal extracts. Herbs also reduce Aβ aggregation and AChE inhibitory activity. However, the FDA has authorized just a few drugs for the treatment of AD [6]. Phytochemicals found in plants have shown promise in treating AD in recent research. The anti-AChE, anti-oxidant, anti-inflammatory, and neuroprotective qualities of several plant families are explored in relation to the therapeutic potential of these various plants.

Role Of Specific Plants And Phytochemicals In Treating Alzheimer's Disease:

Phytochemicals are the chemical molecules contained in plants not usually processed for pharmacological purposes. Phytochemicals influence the function of various receptors for both excitatory and inhibitory neurotransmitters in the brain and thus can maintain or alter the chemical balance of the brain. Several medicinal plants have been used for decades in different cultures to improve memory such as Bacopa monnieri, Centella asiatica, Evolvulus alsinoides, Myristica fragrans, Punica granatum, Salvia officinalis, and Valeriana officinalis. Researchers reported some plants used as anti-aging and memory enhancing activities are Abrus precatorius, Aframomum melegueta, Angraecum eichlerianum, Bacopa floribunda, Bacopa monnieri, Bambusa vulgaris, Baphia nitida, Blighia sapida, Bryophyllum pinnatum, Canna indica, Carapa procera, Carpolobia alba, Capsicum fructescens, Cleome gynandra, Cola acuminate, Cordia millenii, Cucumeropsis mannii, Cuminum cyminum, Dalbergia lacteal, Desmodium gangeticum, Digitaria debilis, Dioclea sarmentosa, Dioscorea mangenotiana, Elaies guineensis, Eleusine indica, Emblica officinalis, Entandrophragma utile, Ficus exasperate, Ficus religiosa, Garcinia kola, Ginkgo biloba, Khaya ivorensis, Ipomoea mauritania, Jatropha curcas, Juglans regia, Melissa officinalis, Milicia excels, Mirabilis jalapa, Musa sapientum, Ocimum basilicum, Parquet inanigrescens, Peperomia pellucid, Piper guineense, Piper nigrum, Rosmarinus officinalis, Spondia smombin, Theobroma cacao, Vernonia amygdalina, , Xylopiaae thiopica, Zea mays. Investigators reported some plants having AChE/BChE activity such as Brassica alba, Brassica nigra, Camellia sinensis, Cinchona officinalis, Citrus aurantifolia, Citrus aurantium, Ferula assafoetida, Humulus lupulus, Juglans regia, Juniperus sabina, Myristica fragrans, Pelargonium graveolens, Pistacia vera, Punica granatum, Rheum officinale, Rosa damascena, Salix alba and Zizyphus vulgaris.

Acorus Calamus: In the Ayurvedic school of medicine, it is a perennial herbaceous monocot wetland plant native to India, Europe, Japan, and China. Phytochemicals in the plant's rhizomes, such as Asarone, cis-isoeugenol, and trans-

isoeugenol, are detected by paper chromatography and validated by direct comparison with real samples. It is used to cure fever, cough, and digestive problems by extracting this herb. With the help of active ingredients in Acetylcholinesterase degradation in the synapses may be inhibited and employed for the treatment of memory-related diseases [7].

Alpinia officinarum: Little galangal (AOH) is a Chinese medicine that warms the stomach and relieves vomiting as well as alleviates the symptoms of colds, flus, and other ailments. Southeast China is home to the Zingiberaceae family's AOH, which is a native of that region. Additionally, AOH has several pharmacological effects that include angiogenesis, antibiotics, anticancers antiinflammatory and vasorelaxation. AOH is a dietary supplement that may be used for therapeutic purposes as well as for its medicinal properties. Diarylheptanoids, such as apigenin and galangin, are the primary phytochemical elements of the rhizome of A. officinarum. Additionally, the active ingredient, Apigenin, may be found in many plants. Toxic effects of A have not been shown in previous research, and it has been shown that apigenin is resistant to A's toxicity. It also possesses anti-inflammatories and antioxidants, and it improves memory and learning problems. Neuronal cells are protected from harm by inhibiting phosphorylation of inducible NOS, COX-2, and p38 mitogen-activated protein (MAPK) in primary microglial cells, according to previous studies. The p38 MAPK and SAPK/JNK signaling pathways were inhibited, as was neuronal death in vitro, in a research that found apigenin to be neuroprotective against Aβ-induced damage. Neuroprotective and immunomodulatory properties of apigenin on glial cells and neurons of Wistar rats were studied. Preserved cell structure and function is achieved by decreasing the expression of OX42 (IL-6), Gp130 (OX42), and TNF-α. Anti-inflammatory and neuroprotective properties of apigenin were also seen when apigenin was administered alone and after an inflammatory stimulation with IL-1. apigenin also reduced BACE1 and β-CTF levels, so decreasing the load of A on the brain and reducing APP processing. The neurotrophic ERK/CREB/BDNF pathway was re-established in the cerebral cortex by apigenin, which may help in the prevention and/or treatment of AD. Drugs that suppress the enzyme AChE are an important class of medications for the treatment of AD. One of the most potent inhibitors of AChE activity, galangin is a flavonoid discovered in rhizome A. officinarum [8].

Alpinia oxyphylla: As a medicine and food, Alpinia oxyphylla Miq. (AOM) is obtained from the ripe and dried fruits of A. oxyphylla Miq. of the Zingiberaceae family. Excessive perspiration, persistent diarrhea, and enuresis may all be treated with AOM, an astringent herb that works to stop the flow of urine when the qi in the body is unstable. Systematic progress on AOM's anti-AD mechanism was recently published. As a result of its ability to inhibit Aβ synthesis and tau phosphorylation, increase antioxidant capacity, reduce inflammation, and prevent apoptosis while also inhibiting AChE activity, researchers believe that AOF has great therapeutic potential for the treatment of AD. LPS-induced learning and memory impairments were reduced by AOM extracts because of their inhibitory impact on neuroinflammation, β-amyloid deposition, and p-tau deposition. Both in vitro as well as in vivo research has shown that AOM has the ability to activate and regenerate nerves by increasing tPA, MMP-9, MAPKs (ERK1/2), and JNK (p38). Research also revealed that treating neurons with AOM extract (80–200 μg/mL) dramatically enhanced cell viability and decreased the number of apoptotic cells, hence exerting neuroprotection. The butanol extract of AOM (180 mg/kg, 360 mg/kg) was also shown to reduce neuronal damage in ICR mice by decreasing β-secretase and Aβ(1–42) levels [9].

Angelica Acutiloba: Divine Farmers Materia Medica contains the traditional Chinese plant Angelica acutiloba Kitag (RAK). Known as "female ginseng," it is a blood tonifying herb that may stimulate blood flow, regulate menstruation, alleviate pain, and treat hernias in women. There are various TCM blood tonics that use RAK (Danggui) as the principal medicinal, such as Danggui buxue Tang (DGBXT), Danggui-Shan (DGSYS), and Fo Shou San (FSS). Astragali radix and Radix astragali are the only MFH ingredients in DGBXT, a traditional Chinese herbal decoction. For the first time, in vitro studies have shown that DGBXT may protect neurons from the effects of β-amyloid by modifying the expression ratio of Bcl2 to Bax and significantly suppressing the Aβ-induced production of apoptotic markers (cleaved-caspase 3/9 and PARP). New research suggests that DGSYS may enhance cognitive function in SAMP8 mice by increasing levels of E_2, NO, and glycine. Researchers found that DGSYS reduced the levels of PEG_2, TXB_2, and LTB_4 and inhibited the expression of cPLA2 as well as COX-1 and COX-2 in an effort to alleviate cognitive abnormalities in APP/PS1 mice in another investigation. Adverse effects of AD have been reduced in APP/PS1 mice by modulating the gut-liver-brain axis and MDA levels in the gastrointestinal tract. Many of the active compounds in RAK and Astragalus aaronii (Eig) Zohary, including as decursinol, vanillic acid, and ligustilide, have been investigated in vivo and in vitro for their therapeutic impact on AD. In ICR mice, Aβ(1–42)-induced impairments in passive avoidance behavior were considerably reduced by pretreatment with decursinol than in control animals. The neuroprotective effect of decursinol on PC12 cells was also mediated through decreasing the mitochondrial mechanism of cell death, as shown in this study. As a result, vanillic acid lowered AChE, TNF-α, and corticosterone in Swiss albino mice, enhancing antioxidants' ability to protect neurons. Both AD-related neuropathological indicators, such as Aβ and amyloid precursor protein and phosphorylated Tau immunoreactivity, and proinflammatory mediators, such as TNF-α and NF-κβ, were considerably improved by Z-ligustilide (40 mg/kg), which was administered to Wistar rats. The p38 and PI3-K/Akt pathways in both SH-SY5Y and PC12 cells may be controlled concurrently by Z-ligustilide, making it resistant to the neurotoxicity caused by β-amyloid. According to recent research, ligustilide has been shown to penetrate the blood–brain barrier in freely moving rat brains, which suggests it might be used to treat AD [10].

Angelica Archangelica: For the treatment of Alzheimer's and other forms of dementia, there are various active ingredients in Angelica archangelica L., or Dudhachoraa (Laghu Coraka). These compounds don't have the negative effects of medicines, such as nausea, stomach discomfort, sleeplessness, and so on. Similar phytochemicals in Angelica

archangelica have been shown to improve cerebral blood flow. chloromethane is shown to inhibit AChE in vitro by an experiment [11].

Astragalus Aaronii: For centuries in China, Astragalus membranaceous var. mongholicus has been utilised as qi-tonifying herbs, which have been shown to have powerful cardiovascular preventive properties. When it comes to the Tiaoxin Recipe and the Fuzheng Quxie Decoction, one of the most important ingredients is Astragalus aaronii (Eig) Zohary (FZQXD). Treatment with the Tiaoxin Recipe reduced the amount of serum Aβ1–42 buildup in APP/PS1 mice serum compared to the normal control group. MicroRNA 34a (miR-34a) expression has also been demonstrated to greatly increase neuronal apoptosis. Mice with the APP/PS1 mutation were given the Tiaoxin Recipe, which drastically reduced the expression of miR-34a in the animals' bodies. FZQXD has been shown in in vivo tests to protect against AD-related neurodegeneration via signalling through VEGF and VEGF receptors. Small molecular weight saponin Astragaloside IV (AS-IV) has been found to have various therapeutic benefits in the prevention and treatment of neurodegenerative illnesses, such as AD and Parkinson's disease. AS-IV protects AO-induced memory loss via increasing the PPAR/BDNF signalling pathway, according to the literature. AS-IV therapy boosted PPAR and BACE1 expression and lowered neuritic plaque formation and A levels in the brains of APP/PS1 mice, which eventually attenuated the creation of A, according to an in vivo investigation. For the prevention and treatment of neurodegenerative illnesses such as AD, AS-IV pretreatment reduced Aβ1–42-induced SK-N-SH cell death by reducing mPTP opening and ROS production [12].

Bacopa Monnieri: Bacopa monniera (Bhrami) has been utilised for millennia in the Ayurvedic medicine system in India. The Ayurvedic medicinal system has traditionally used it to relieve anxiety, as a brain tonic to improve learning and memory, and to prevent epilepsy. Different tissues experience different levels of degenerative changes as they age, and these changes are determined by their architecture and physiology. Oxidative damage to DNA and a hormone deficit are two mechanisms that contribute to these alterations. Hormones and neurotransmitters must all work together in order for the body's stress response to be normal. The therapeutic benefit of Bacopa is due to the presence of several alkaloids, such as asbrahmine and herpestine, saponins, d-mannitol, hersaponin, and monnierin. Betulic acid, stigmastarol, β-sitosterol, various bacosides, and bacopasaponins are among the other active ingredients. Synaptic activity may be restored, kinase activity is increased, and neuronal synthesis is stimulated by the bacosides. Repairing neurons is an important part of treating AD. Protein kinase activity in the hippocampus may contribute to its nootropic effect, which signifies an increase in cognitive performance. β-Amyloid-induced cell death is prevented in neurons by Bhrami extracts, which reduce cellular acetyl cholinesterase activity. Choline acetyl Transferases were reduced, and muscarnic cholinergic receptor binding in the frontal brain and hippocampus was decreased [13].

Bertholettia Excelsa: Despite their common name, Brazil Nuts are mostly exported from Bolivia, not Brazil. Castanhas do Para (Brazilian castanhas) are a kind of nut native to Brazil. Choline is abundant in lecithin, which is abundant in this product. Acetylcholine may be synthesized from choline, which is a necessary building component. In individuals with AD, acetylcholine levels are boosted by the use of these building blocks. Dandelion blossoms, poppy seeds, soybeans, mung beans, horeroos, ginseng, horehound, cowpeas, English peas, and lentils are all rich sources of lecithin [14].

Celastress Panicultus: Unani and Ayurveda employ it as a traditional remedy since it grows across India. The cholinergic action in the seeds of this plant helps to strengthen the memory. It enhances medhya-guna, or memory power, and almonds, cardamom, Jatamanasi, and Shankhpushpi are used in conjunction with it to achieve this goal. Alkaloids are found in the stem component of the plant, including Winfornine-F and Paniculatine-A and Paniculatine-B, while Celastrine, Celapagine, Celpanigine, and Celapanine are found in the seed. Hydrogen peroxide driven cell death may be prevented in part by the antioxidant enzymes included in the extract, which can also improve memory function by increasing the amount of dopamine in the brain. The anti-cholinesterase activity and cholinesterase inhibitory impact of the organic methanolic fraction of seed extract were shown to be significant with regard to IC_{50} values [15].

Centella Asiatica: Perennial flowering plants native to Asia are utilized as both a culinary ingredient and a medicinal herb. Asiatic acid and Asiaticoside derivatives, such as Asiatic acid and Asiaticoside, have been demonstrated to reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and prevent β-amyloid cell death in a variety of animal studies. This plant's water extract has been found to reduce Aβ-induced cell death and change Tau expression and phosphorylation in cell lines. According to a study by the Alzheimer's Drug Discovery Foundation (ADDF), it may lower oxidative stress and prevent neuronal process atrophy. Lipid peroxidation is reduced, and DNA is protected from damage, when this plant's extracts are used. Brain and nerve cells need this plant, and it's capable of improving intelligence and creativity [16].

Cissampelos Pareira: Menispermaceae is the family of Cissampelos pareira. It was tested on mice to see whether it affected their memory and learning. Passive avoidance paradigm and raised plus maze were used to measure memory and learning. One hundred, two hundred, and four hundred mg/kg of C. pareira hydroalcoholic extract were administered orally to rats for seven days. In mice, C. pareira 400 mg/kg increased memory and learning greatly. At 400 mg/kg of C. pareira extract, amnesia caused by scopolamine was reversed. Increasing antioxidant and anti-inflammatory activity and reduced AChE activity are two possible explanations for C. pareira's nootropic effects [17].

Cistanche Afghanica: Because of Herba Cistanches' ability to strengthen the kidney, restore vital essence and blood, and induce taxation as a tonic herb, it has acquired the nickname "Ginseng in the deserts." Yin-tonifying medication in China, Herba Cistanches, has a wide range of therapeutic properties, including immunomodulation, endocrine control, hepatoprotection as well as the ability to fight against ageing, germs, viruses, and tumours. Herba Cistanches have been recognised as having considerable promise in the therapy of age-related disorders in recent years. While limiting Aβ1–42 amyloid deposition and lowering P-tau phosphorylation were the most important mechanisms, inhibiting NO production was also a factor, as was influencing the signalling route between ROS and activating Ca2+ channels. A different approach is to use Herba Cistanches, which has been shown to induce neuroprotection by causing cell cycle arrest and apoptosis, increasing the expression of anti-apoptotic proteins, and promoting intestinal epithelial cell proliferation while also increasing the levels of TGF-α and CRMP-2 protein expression. Phenomenal glycosides from Cistanches salsa (10, 50 mg/kg) were also reported to protect C57 mice against dopamine neurotoxicity produced by 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine. Echinacoside, a phenylethanoid derived from the stems of C. salsa, was shown to have antiapoptotic and anti-inflammatory characteristics, which was another intriguing result. Inflammatory mediators such as TNF-α, IL-1, and IL-6 were considerably reduced after pretreatment with echinacoside. Tubuloside B, a phenylethanoid found in C. salsa stems, also possesses neuroprotective properties, including antioxidative stress and antiapoptotic activities. It was later shown that tubuloside B (1 mg/L, 10 mg/L, or 100 mg/L) reduced TNF-α-induced apoptosis and ROS and $[Ca^{2+}]I$ buildup in SH-SY5Y neuronal cells. Neuroprotective benefits of Cistanches herba were studied in individuals with intermediate AD. C. herba may have neuroprotective benefits in mild AD by lowering levels of T-tau, TNF-α, and IL-1, according to their research [18].

Collinsonia Canadensis: Studies have shown that the herb horsebalm (Monarda) helps to keep acetylcholine from degrading. Carvacol and thymol, two of horsebalm's most important chemical components, are utilised in the treatment of AD. Our body's blood–brain barrier is designed to keep dangerous chemicals from entering the brain's tissues. The problem is that it may also impede the delivery of beneficial drugs to the human brain. Horsebalm compounds, on the other hand, appear to span that enormous chasm. Adding a few drops of horsebalm to your regular herbal shampoo may also serve as a herbal shampoo [19].

Commiphora Wightii: Guggul is a popular name for this plant, which grows well in dry and semi-arid areas and is tolerant of poor soil. In Unani and ayurvedic medicine, it works well. There are several phytochemicals found in gum guggul extract, including diterpenoids, triterpenoids and steroids as well as long-chain aliphatic tetrols and polysaccharides. In the Streptozotocin-induced memory loss model of dementia, Guggulipid has a considerable protective effect, and the effect may be related to its cholesterol-lowering, anti-oxidant, and anti-AChE activities. Impaired learning and memory, and reduced AChE in hippocampus are some of the effects of this drug [20].

Convolvulus Pluricaulis: Known as shankhpushpi, this species is native to India and Burma, where it is utilised in traditional Ayurvedic treatment. Coumarines (Shankhpushpi), Glycosides and flavonoids are some of the phytochemicals found in the whole plant, as well as Sitosterol, Hydroxy cinnaminic acid and Tetracosane. It's been used for a long time as a brain tonic, sedative, and phytostimulant. It is the greatest and most effective tonic for boosting memory and treating dementia, OCD, phobias, and insomnia. Stress hormones, Adrenaline and cortisol, are regulated by it. Rats' learning and memory were considerably enhanced by ethanolic extracts, ethyl extracts, and aqueous fractions. Treatment with acetyl cholinesterase increased activity in the hippocampus, a part of the brain involved in both learning and memory [21].

Crocus Sativus: The Iridaceae family includes Crocus sativus. C. sativus is becoming more popular as a therapy for AD and memory loss. C. sativus was studied in 55-year-olds throughout a 22-week period in clinical studies. Capsule saffron 30 mg/d or donepezil 10 mg/d were given to patients in a random order. After 22 weeks of therapy, it was shown that C. sativus 30 mg/d was equally effective as donezepil in individuals with mild to severe AD. Saffron-treated and donezepil-treated individuals had comparable rates of side effects, except for vomiting, which was more common in donezepil-treated patients. Saffron extract was compared to memantine in a comparable trial aimed at reducing cognitive decline in people with moderate to severe AD. A year's worth of saffron extract (30 mg/d) or memantine (20 mg/d) was administered to 68 individuals in this research experiment. Patients were assessed monthly using the Functional Assessment Staging and the Severe Cognitive Impairment Rating Scale, and any negative effects were noted. Patients with moderate to severe AD were shown to benefit from C. sativus at 30 mg/d after one year of therapy. In both treatment groups, there was no significant difference in the incidence of side effects [22].

Curcuma Longa: Turmeric has been utilized in Ayurveda, Siddha, Unani, and traditional Chinese medicine throughout Asia for thousands of years. To date, India has been the world's most significant producer, exporter, and consumer of turmeric. It is a perennial herbaceous plant that grows year after year. 6-13 percent water; 6-8 percent protein; 3-7 percent essential oils; 2-7 percent fibre; 1-6 percent curcuminoids are found in the turmeric powder. Curcumin has been shown to be effective in the treatment of AD and other forms of dementia. In addition, it has the capacity to postpone the deterioration of neurons, which are both hallmarks of AD. AD sufferers' general memory is enhanced free radical generation and propagation are inhibited by curcuminoids, demonstrating their potent antioxidant effect. Reduces the oxidation of low-density lipoprotein and the production of free radicals, both of which contribute to the degeneration of neurons in Alzheimer's and other neurodegenerative diseases including Huntington's and Parkinson. Low dosages of curcumin reduced β-amyloid levels in AD animals by around 40% as compared to mice that were not given curcumin.

The so-called "plaque load" that β-amyloid has on the brains of AD mice was likewise reduced by 43% by modest dosages of curcumin. Over a longer time, modest dosages of curcumin proved to be more efficient than high doses in preventing the neurodegenerative process of AD. At greater concentrations, curcumin binds to β-amyloid and blocks its self assembly [23].

Evolvucus Alsinoides: Slender dwarf morning glory is a frequent name for this blooming plant. It may be found in tropical and temperate locations around the globe, including the Americas, Africa, Australia, and Indo-Australia. It is considered one of Kerala's ten holy flowers, Evolvucus alsinoides (Dasapushpam). Because of its psychoactive and nootropic properties, it is often prescribed as a traditional medicine in East Asia. Scopoletin, scopolin, umbelliferone, and 2-methyl-1,2,3,4-butanetertrol are among the plant's phytochemicals [24].

Ficus Racemosa: Ficus racemosa is a member of the Moraceae family. F. racemosa (250 mg/kg and 500 mg/kg) dramatically enhanced acetylcholine levels in the rat hippocampus, where the memory-enhancing effects of F. racemosa bark in rats was studied. Patients with AD may benefit from this therapy because of the promising results of this research [25].

Galanthus Nivalis: Native to Spain, Ukraine, and France, and commonly grown throughout Europe, this perennial plant germinates from blubs. Along with Glantamine and Lectin or agglutinin, alkaloids (Tazettine, Pretazettine) are also found in the plant It's a large-volume medication with little protein binding. Due to its allosteric modulator function, Glantamine increases the levels of Glutamine, GABA, and Seratoine, which enhances Ach's effects on learning and memory by activating Nicotine receptors. Because it effectively restores cognitive impairments in rat models, it may be utilised as a cognitive enhancer [26].

Ganoderma Lucidum: Ganoderma lucidum (Leyss.ex Fr.) Karst., a basidiomycete white rot microfungus widely utilised in China for 2000 years, is also known as "the mushroom of immortality." As a qi-tonifying medicinal in ancient times, G. lucidum was used to cure qi deficiencies. In addition to its antibacterial, antiaging, antiviral, and antiangiogenic activities, G. lucidum has antioxidative, antiinflammatory, and analgesic qualities. G. lucidum has been shown to alleviate symptoms of nervous system damage and neurotoxicity in patients with low levels of the Aβ-40 protein and high levels of ApoA1, ApoE, and Syt1. G. lucidum's aqueous extract was shown to reduce phosphorylation of c-Jun, N-terminal kinase, c-Jun, and p38 MAPK kinase, preventing Aβ-induced synaptotoxicity. TLR signalling pathways in activated microglia were blocked by EGL in neurodegenerative disease therapy, which reduced inflammation in active microglia. It has been shown that EGL has a possible neuroprotective impact by reducing IB degradation and TLR4 and MyD88 expression in LPS-stimulated BV2 cells, which displayed its anti-inflammatory action. EGL increased the antioxidant defense capability of C2C12 myoblast cell line by raising the expression and phosphorylation of Nrf2 and HO-1. FGFR1 activation and ERK and AKT inhibition by G. lucidum polysaccharide have been shown to increase cognitive function and brain progenitor growth in vitro. Trichloroacetic acid (TCA) and other G. lucidum triterpenoids decreased APP/PS1 mouse brain damage by reducing oxidative damage, preventing apoptosis, and inactivating the rise in ROCK1 and ROCK2 in the hippocampus. G. lucidum aromatic components have anti-inflammatory properties with IC50 values of between 4.68 μM and 15.49 μM in RAW264.7 macrophages [27].

Ginkgo Biloba: Native to China and Japan, it is generally known as Ginkgo biloba; it is the sole species in the ginkophyta genus, and it is used in a variety of medicinal and culinary applications. They include phenolic acid, proanthocyanidin, flavonoid glycoside (Myricetin), kaempferol, isohamnetin, and quercerine, as well as terpens and biobalides. Ginkgo biflavone and alkylphenols are also present in the extract. AChE activity in the brain is considerably inhibited by the flavonoids and terpenes in the extract. A powerful anti-oxidant with cholinergic and neuroprotective properties, Ginkolides are the primary chemical ingredients of Ginseng, which protects against the oxidative damage caused by Aβ-protein. Many molecular pathways have been identified, including the suppression of apoptosis, reduction of membrane lipid peroxidation, and anti-inflammatory actions [28].

Huperzia Serrata: In the Huperziaceae branch, Huperzia serrata (Thunb. ex Murray) is one of the genus (syn. Lycopodiaceae family). Lycopodium alkaloids, a group of alkaloids found in this genus, have been utilised in Traditional Chinese Medicine (TCM) for centuries for their memory-enhancing properties. New Lycopodium alkaloid Huperzine A from H. serrata has long been recognized as a reversible, powerful, and specific AChE inhibitor. China has long employed Huperzine A as a treatment medication for AD, and it is also known as "Qian Ceng Ta." Huperzine-A has been shown to boost memory, focus, and learning ability, according to experts. Huperzine-A has also been demonstrated to significantly lower the abnormally high radical activity in the brains of aged animals and the blood of Alzheimer's patients, according to the findings of research. Patients with dementia or Alzheimer's may benefit from this treatment because of research in monkeys showing that it restores the amnesia caused by scopolamine [29].

Ilex Paraguariensis: The Aquifoliaceae family includes Ilex paraguariensis. As a result, it enhances memory. Vitamin B12, B1 and C are included in this supplement. The anti-dementia agent is derived from I. paraguariensis. It was tested in a variety of rat models for its memory-enhancing properties. The memory-enhancing properties of I. paraguariensis have

been documented. Memory may be improved by using I. paraguariensis in the treatment of vascular dementia. I. paraguariensis has been shown to be beneficial in the treatment of neurodegenerative illnesses including AD [30].

Lepidium Meyenii: The Brassicaceae family includes Lepidium meyenii. Learning and memory function are enhanced by Maca, a supplement. Patients with AD who took L. meyenii reported improved memory after taking it. Acetylcholine, a neurotransmitter involved in memory, is elevated when this supplement is taken. Because of its AChE inhibitory and antioxidant properties, it improves experimental memory impairment caused by ovariectomy. In ovariectomized mice, L. meyenii improved memory and learning, which the researchers believe is at least in part due to the herb's capacity to reduce lipid peroxidation and AChE in these animals [31].

Lycium Barbarum: There is mention of Lycium barbarum L. in Shennong Ben Cao Jing, a yin-tonifying medicine from the Solanaceae family that is a "berry-type" fruit of L. barbarum L. Phytochemical components of Fructus lycii and its anti-AD effects on oxidative stress, anti-immune function, anti-apoptosis and antinecrosis have been studied extensively in recent years. Extracts from F. lycii reduced the toxicity of fibrillar Aβ(1–42) and Aβ(25–35) fragments on neuronal loss and behavioral deficits. Caspase-3 activity was improved by 11.8 percent using extracts of F. lycii (100 μg/mL) as compared to the Aβ peptide-treated group in an in vitro investigation, researchers discovered. The protein levels of JNK, c-Jun, and β-actin were considerably reduced by pretreatment with F. lycii extract at 100 μg/mL, although the protein levels of total JNK, total c-Jun, and β-actin were unaffected by LBA. β-Sitosterol, caffeine, and zeaxanthin are just a few of the antiaging compounds found in F. lycii, according to research conducted. Adaptability to oxidative stress has been linked to an organism's ageing and lifespan by researchers. A good antioxidant is Fructus lycii polysaccharides. Dietary zeaxanthin, according to a comprehensive review and meta-analysis, may help prevent age-related macular degeneration. According to a brief review, the anti AD therapeutic potential of caffeic acid is linked to antioxidant activities, particular anti-inflammatory brain mechanisms, and diverse β-amyloid production processes [32].

Magnolia Officinalis: Higher-elevation Chinese highlands and valleys are home to a variety of Houpa magnolia species. Magnolol, Honokiol, and Two Polyphenolic substances are found in the bark. GABA modulation and peroxisome-proliferator activated receptor gamma agonistic activity (PPAR Gamma) have been found in this plant. An anti-inflammatory agent and an antibiotic are only a few possible applications for this compound. Adding two Magnolia officinalis extract products (10 mg/kg/day in ethanol) to drinking water for three months improved memory impairment and avoided the formation of Aβ. The amyloid precursor proteins and their metabolites were also reduced in the extracts. As a result, it may be used to treat and prevent AD by improving memory. The level of neuroprotective effectiveness and the degree to which β-secretase activity may be downregulated influence the herb's anti-amyloidogenic properties [33].

Matricaria Chamomilla: In low-lying parts of India, the Americas (North and South), and Australia, this annual plant grows as a weed as a weed. It contains terpinoids such β-bisbolol, β-bisbolol oxide A, and β-bisbolol oxide B and sesqueterpenes, luteolin, coumarins, umbelliferone, and polysaccharides. To use this plant as a herbal remedy for AD, it is important to understand the plant's phytoconstituents and their role in neuroprotection and antioxidation [34].

Matricaria Recutita: German Chamomile is considered to be a brain stimulant, a fatigue dispelling agent, a nerve relaxant, an anti-insomnia help, a digestive aid, a mucus breaker, and an immune system booster. A study found that chamomile may ease anxiety and induce sleep when taken in greater amounts [35].

Melissa Officinalis: Native to southern Europe, Central Asia, and the United States, it is a perennial plant having culinary and therapeutic purposes. Eugenol, citral-α and citral-β, tannis, terpenes, citronellal, harmine traces, and rosemaric acid are among the plant's chemical ingredients. Toxic compounds found in this plant's leaves, such as monoterpenes (also known as "ex-citral"), have been shown to have mild anti-AChE activity, while the phenol carboxylic acids in the leaves have been shown to have anti-oxidant, anti-amyloid, and anti-apoptotic properties [36].

Morinda Citrifolia: There are several therapeutic uses for the various parts of the tree, which are extensively grown throughout Asia and Australia. Polynesian and traditional cultures used them as a Tonic and famine food, but few regulatory agencies have approved skincare products made from it. Chemical constituents include alkaloids, lignans, oligo and polysaccharides, flavanoids, as well as carbohydrates, dietary fibers, vitamin A, B3, C, Iron, potassium, and dietary fiber. Noni juice has been shown to have anti-cancer, anti-inflammatory, and oxidation of LDL properties in animals that have been given it. Based on how old a portion is, the extract's anti-oxidant efficacy changes, as well as its ability to sabotage the metabolism of AChE [37].

Myristica Fragrans: The Myristicaceae family includes Myristica fragrans. β-sitosterol, myristic acid, lauric acid, pentadecanoic acid, palmitic acid, heptadecanoic acid, stearic acid, oleic acid, and elemicin are some of the compounds that make up this mixture of camphene, β-pinene, and sabinene. Medicinal uses for M. fragrans include the treatment of neurological and gastrointestinal diseases, as well as the treatment of leukaemia, body aches and tachycardia. It is hypolipidemic, depressive, antioxidant, and antibacterial in nature. There were three different doses of the n-hexane extract of M. fragrans given to young and old mice for 3 consecutive days: 5 mg/kg, 10 mg/kg and 20 mg/kg. Scopolamine and diazepam-induced memory and learning impairments were reversed by this medication at a dose of 5 mg/kg. The usage of M. fragrans in the treatment of AD and memory loss was shown to be effective in this research [38].

Nardostachys Jatamanasi: A blooming plant generally known as muskroot or spikenard, it is grown in Nepal, Sikkim, and Bhutan for its medicinal properties. The essential oils from this plant, which have a strong scent and are amber in colour, are utilised in perfumes. acaclin, ursolic acid, octacosanol, nardosinonediol, oleanolic acid, and β-sitosterol are among the plant's chemical ingredients. Young and old rats given an alcoholic extract of this plant showed dramatically better learning and memory, and the amnesia caused by diazepam and scopolamine was also reversed by the extract. There is evidence that the component in this plant may be effective in patients with age-related dementia, as well as in older persons, since it restored aging-induced forgetfulness in rats [39].

Panax Ginseng: Panax root is the product. A variety of ginsengs, including Korean ginseng, South China and American kinds are widely grown. Peptides, ginsesenosides, polyacetylenolic alcohol, polyacetylenic alcohols, polyacetylenic fatty acids, and polysaccharides are all phytoconstituents of this plant, which have been shown to improve memory in people with learning disabilities caused by scopolamine. By increasing brain Cholinergic function, lowering AD levels, and rebuilding the damaged neural network, ginseng is able to improve psychomotor and cognitive performance and benefit AD [40].

Piper Nigrum: Piper nigrum L. is a tropical tree whose fruits are used to make spices and seasonings and as a functional food. Its fruits are widely dispersed. Interior-warming TCM medication P. nigrum helps alleviate stomach cold and remove phlegm. Antioxidant, antibacterial, and insecticidal effects have all been studied extensively in modern pharmaceutical research. Using AD-induced rats, it was discovered that P. nigrum whole plant extracts dramatically increased Ach, serum total antioxidant capacity (TAC), and SOD while considerably reducing AchE, MDA, and NO, all of which contribute to neurodegeneration. Methanolic extracts of P. nigrum (50 mg/kg and 100 mg/kg) restored the activity of SOD and Catalase (CAT) in the hippocampus of A(1–42)-treated rats and boosted GPX activity. In hippocampus homogenates, methanolic extract (50 mg/kg and 100 mg/kg) lowered protein carbonyl and MDA levels while simultaneously increasing GSH levels as an antioxidant agent. There is 51.12% of the P. nigrum essential oil's composition made up of β-caryophyllene, according to GC and LC-ESI-MS (EO). By lowering inflammation and reducing the β-amyloid load, β-caryophyllene may ameliorate the Alzheimer-like phenotype. They found that lowering the β-amyloid load in the hippocampus and cerebral cortex with β-caryophyllene reduced cognitive impairment in APP/PS1 mice. The proinflammatory cytokines TNF-α and IL-1 were also lowered by β-caryophyllene in the cerebral cortex, as were the protein levels of COX-2. The researchers in this study also looked at the potential that β-caryophyllene might help cure AD by activating CB_2 receptors and the PPAR pathway in APP/PS1 mice. Some metal ions or alcohol have long been known to cause β-synuclein to aggregate in vitro. Curcumin and β-caryophyllene have been shown in several trials to not only suppress β-synuclein aggregation but also dissolve preexisting clumps nearly entirely at low concentrations. Piperine, an alkaloid found in black pepper (Piper nigrum), has been demonstrated to have anti-inflammatory, antioxidative, cholinergic neuronal transmission, antidepressant, and antipyretic properties. Piperine substantially improved cognitive impairments by reducing oxidative state in comparison to AD-Tween-treated groups. Memory impairment and neurodegeneration in the hippocampus were alleviated by piperine at varied dosages of 5 mg/kg, 10 mg/kg, and 20 mg/kg, which was mostly due to a reduction in lipid peroxidation and the AChE enzyme. Piperine's in vitro AChE inhibition was shown to be stronger, with an IC_{50} of 76.6 μg/mL in the SH-SY5Y cell model of AChE inhibition. Combining piperine with the anti-inflammatory properties of curcumin has also been shown to reduce oxidative damage and decrease fibril formation in mice [41].

Rosmarinus Officinalis: Rosemary, a shrub native to North Africa and Spain, is often used as a culinary seasoning and in perfumes. It's an excellent source of iron, calcium, and vitamin B_6. Polyphenols (e.g. limonine) and monoterpenols are the chemical ingredients of the odorant. This plant's essential oil contains 1, 8-cineole, which is why it is used in Aromatherapy to stimulate the body and brain and improve cognitive function. Acetylcholine, an essential brain neurotransmitter, is degraded in the presence of specific phytochemicals in the plant. For the most part, persons with AD have low levels of this molecule [42].

Salvia Officinalis: An evergreen subherb native to the Mediterranean area, it may be found all over the globe and thrives in a variety of soil types. This herb has been used for centuries for medical, traditional, decorative, and culinary purposes alike. The Phytochemicals in the plant make it more unique in treating different infertility issues, diuretics and local anaesthesia for skin, styptic, anti-oxidant disorders. 1,8-Cineole, camphor, α-thujone and β-thujone, vridiflorol, and α-pinene are some of the ingredients in this mixture. After four months of administering a fixed dosage of 60 drops/kg extract to patients in mild to moderate stages of AD, the research found that these individuals were free of agitation for the rest of their lives. Because of the rosmarinic and carhosic acid in this extract, it also protects the brain from oxidative damage [43].

Serrate Clubmoss: The serrate clubmoss plant contains a strong, reversible, and specific AChE inhibitor, huperzine A. Huperzine A seems to have some good benefits on the improvement of general cognitive function, global clinical status, behavioral disturbance and functional performance, with no clear major adverse events for people with AD, according to the data from six studies available. There was just one high-quality and large-scale trial, however the span of time during which this study demonstrated strong treatment benefits lasted only 12 weeks. Huperzine A's therapeutic utility is now hampered by a paucity of compelling data [44].

Tinospora Cordifolia: A warm temperature and red or black soil are ideal for this perennial herbaceous plant, which is native to India, Myanmar, and Sri Lanka. Seeds and cuttings may be used to propagate plants. Steroids, alkaloids, polysaccharides, and glycosides are among the plant's phytoconstituents. The plant's anti-oxidant action makes it effective as a medicinal herb for the treatment of AD [45].

Utrica Dioica: Typically growing as a weed in farmland, it is a perennial herb used in veterinary folk medicine. Combining this herb with others or using it on its alone may cure a wide range of illnesses or issues relating to infertility, breastfeeding, or the proper functioning of internal organs. Lignans, isolecthins, terpenes, proteins, vitamins, minerals, flavanoids, and tannins are the chemical components of this. Methanolic extract of this plant, 0.5 g/kg for 30 days, exhibits immunosimulatory effect and is utilized for the development of ornamental fish. With regular exercise and the use of this plant extract, rats' brain lesions may be reduced [46].

Vitis Vinifera: A deciduous, woody blooming plant native to the North East, it is a popular ornamental plant there. Table grapes may be eaten fresh or processed into a variety of products, including wine, jam, jelly, extracts, seed oils, and raisins. Green, pink, orange, yellow, dark purple and black fruits may be found on these bushes. The amount of Anthocyanins and other polyphenolic pigments in red wine determines the colour of the wine. As part of a plant-based diet, grape polyphenols have been shown to enhance cognition and protect the brain by enhancing vascular health and function as well as signaling neurotransmitters and lowering hazardous oxidation, all of which are connected to decreased risk of cognitive decline [47].

Withania Somnifera: There are a variety of chemical ingredients in Ashwagandha or Indian ginseng, including alkaloids, steroidal lactones, saponins, and more. It has been utilized as a medicinal herb in Ayurveda for centuries because of its wide range of applications. A variety of ailments, including arthritis, impotence, amnesia, cancer and neurological disorders may be treated and prevented by the bioactive component and the plant extracts. Rejuvenation of the nervous system, bone marrow, and reproductive system are all possible with this supplement's use. It has been shown that Ashwagandha may enhance cognitive performance in rats exposed to the oxidative damage that occurs in AD and that it can reverse the buildup of β-amyloid peptides, which are involved in this disease's onset. Withania somnifera has been shown to reduce oxidative damage, enhance toxic Aβ clearance, and reduce neurodegeneration, according to studies. W. somnifera's mode of action in humans is unknown. Sitoindoside VII-X and Withaferin A (glycowithanolides) are the active phytophenols responsible for the mechanism of enhanced cortical Muscarnic acetylcholine capacity, with a modification of cholinergic neurotransmission, in animal studies, According to these investigations, W. somnifera usage may alter brain function. It was found that Withanamide-A and Withanamide-C were modeled in molecular simulations. Prevent fibril production by binding to the active moiety of β-amyloid. Both the aqueous and methanol extracts of human neuroblastoma cells stimulate cholinergic activity in dosage and time dependent ways. According to the research, it might be used therapeutically to prevent and perhaps heal problems of the central nervous system [48].

Zingiber Officinale: The fresh rhizome of Zingiber officinale Roscoe (ZOR) traced from Shen Nong Ben Cao Jing is Z. officinale Roscoe. ZOR is listed in the Chinese Pharmacopoeia as an anti-cold, anti-vomiting, anti-phlegm, and anti-cough medicine that may induce sweating and dispel colds. As an antioxidant, anti-inflammatory, antidiabetic, anti-nausea, neuroprotective, and cardiovascular protective substance, ZOR is extensively utilized in traditional medicine. In the treatment of AD, several studies have shown that ginger's anti-inflammatory properties improve cognitive function. NF-κB and IL-1 expression levels were lower in the high dosage (4 g/kg) groups of ginger root extract than in the moderate dose (2 μg/kg) and low dose (1 μg/kg) groups of ginger root extract, according to data from the SD rat model. Wistar rats' hippocampi showed considerable suppression of GFAP and IL-1 expression by ZOR extracts at a level of 200 mg/kg in subsequent trials. A methanolic extract of dried ginger was tested for its antioxidant and cholinesterase inhibitory activities. It had 18.6 mg/g equivalents of gallic acid and 4.18 mg/g of quercetin equivalents in the total phenolic extract and dry material. To test for antioxidant activity, they discovered that in the DDPPH assay it was found to be 70 mg/mL and in the FRAP assay it was found to be 854 mg/g dry weight of ferrous iodide equivalents per gram of dry weight. Also, they observed that GE had an IC_{50} value of 41.1 μg/mL for AChE inhibition and 52.2 μg/mL for BChE inhibition in Ellman's test, respectively. Water-extractable red and white ginger reduced AChE activities in a dose-dependent manner, and white ginger showed a greater AChE inhibitory effect than red ginger. When combined with sodium nitroprusside and quinolinic acid, both extracts dramatically reduced the MDA concentration. There are several pharmacological properties of 6-gingerol, which is a phenolic molecule found in ginger rhizomes, including anticancer, anti-inflammatory, and antioxidant properties. Six-gingerol has been shown to have neuroprotective properties by conducting both in vitro and in vivo studies. Researchers found that pretreatment of PC12 cells with 6-gingerol enhanced cell survival and decreased apoptosis after Aβ1–42 treatment, proving that 6-gingerol has neuroprotective properties. 6-Gingerol was shown to significantly lower ROS and MDA levels in the brains of AD patients, as well as boost the activity of SOD, compared to the Aβ1–42 therapy group. Aβ1–42 increased p-Akt and p-GSK-3 levels, which were further boosted by pretreatment with 6-gingerol. 6-Shogaol dose-dependently alleviated obesity and emotional memory impairments in a rat C57BL/6N mice model produced by a Western diet rich in fat and sugar (HFSD). 6-shogaol at a dose of 10 mg/kg substantially increased NGF, PSD-95, and synaptophysin expression levels in hippocampus tissues compared to the vehicle-treated group in an ICR mouse model [49].

Ziziphus Jujuba: Ziziphus jujuba Mill. (SJM) is mostly found in northern China's interior, where the old Chinese proverb "thorns are everywhere" applies. Traditional Chinese Medicine (TCM) prescribes SJM, a popular heart-nourishing medicine in China, as a means of calming the mind. In addition to its anti-inflammatory and anti-complementary characteristics, SJM also has hematopoiesis-promoting, antioxidant stress-relieving, and anticancer capabilities. SJM is commonly employed in current pharmacology research studies to reduce symptoms similar to those of AD. Oral administration of SJM to 5XFAD mice improved memory deficits by increasing plasmin levels and activity in hippocampal slices from 5XFAD mice, according to the available data. Furthermore, in the hippocampus of CD-1 mice, SZS has been shown to improve Aβ-induced LTP deficits through BDNF/TrkB signalling and to increase plasmin activity. SJM's flavonoid extract may help Caenorhabditis elegans recover from Aβ-induced toxicity, according to new research. As a C-glycoside flavonoid, Spinosin is found in the seeds of SJM and has anxiolytic and hypnotic properties, as well as a positive impact on cognitive function and memory loss. The ERK-CREB-BDNF signaling pathway was stimulated by subchronic illness therapy with spinosin (5 mg/kg) to alleviate cognitive impairment in the hippocampus. It was shown that spinosyn inhibited Aβ1–42 synthesis by activating the Nrf2/HO-1 pathway in Neuro-2a cells (N2a/WT) and N2a/APP695 cells in vitro. The modulation of oxidative stress, inflammation, apoptosis, and the action of the protein plasmin by spinosin may also help alleviate learning and memory problems [50].

Concerns About Herbal Anti-Alzheimer's Disease Agents:

The effectiveness, safety, purity, and probable medication interactions of herbal therapies are not understood, which raises concerns about taking these products as an alternative or supplement to contemporary medicine. In contrast to the FDA's clearance process for prescription drugs, dietary supplement laws don't need the same level of rigorous scientific study. Dietary supplement manufacturers don't require to submit the FDA with proof of their product's safety and efficacy. As a side effect, this might lead to the presence of harmful substances in the supplement. Dietary supplement health and education act of 1994 gives FDA jurisdiction to take items off the market if it can establish that they are adulterated (e.g., hazardous) or misbranded under existing FDA regulation (e.g., that the labeling is false or misleading). Nutritional supplements may interfere with prescription drugs if they are not used in moderation. The purity and safety of herbal products may be guaranteed if the FDA demands clinical studies and rigorous quality inspections prior to their release to the market. Further research after the product has been released should be encouraged to look for any negative consequences. Labeling guidelines state that anybody considering using herbal supplements should speak with their pharmacist or physician beforehand [51].

CONCLUSION:

Alzheimer's disease and other illnesses characterized by memory loss and dementia may be helped in the early stages of therapy by herbal remedies. A major advantage is that they are less harmful than pharmaceuticals. For example, SAMe, fish oil, and antioxidant vitamins may all be utilised in conjunction with botanicals to treat a variety of conditions. Treatment should begin as soon as possible, according to an assessment of the literature. As a result, individuals with a family history of Alzheimer's disease or other conditions characterised by memory loss may choose to begin taking these treatments in order to postpone or perhaps prevent the development of symptoms. Long-term treatments for memory loss, dementia, and Alzheimer's disease, such as the acorus/ginkgo formula (which also contains salvia and gingko), and vinpurazine (which contains naturally derived huperzine A), seem to be very promising. The use of herbal remedies in the treatment of Alzheimer's disease should be compared to the present pharmaceutical therapy. In order to increase the validity of the clinical trial, such investigations should identify the active principle. The efficacy of these compounds in slowing the cognitive decline associated with Alzheimer's disease requires further large-scale, multicenter research. A broad variety of herbs (from the Indian Medicine System, the Chinese Medicine System, and the European Medicine System, among others) have been shown to be beneficial in the treatment of Alzheimer's disease.

CONFLICT OF INTEREST:

None declared.

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REFERENCES:

1. Russo P, Frustaci A, Del Bufalo A, Fini M, Cesario A. Multitarget drugs of plants origin acting on Alzheimer's disease. Curr Med Chem. 2013;20(13):1686-93.
2. Hajiaghaee R, Akhondzadeh S. Herbal medicine in the treatment of Alzheimer's disease. J Med Plant. 2012;11(41):1-7.
3. Howes MJ, Perry NS, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. Phytother Res. 2003;17(1):1-8.
4. Roy A. Role of medicinal plants against Alzheimer's disease. Int J Compl Alt Med. 2018;11(4):205-8.
5. Sanka N, Santhipriya N, Nadendla RR. An updated review on Anti-Alzheimer's herbal drugs. J Drug Deliv Ther. 2018;8(6):360-72.
6. Menghani YR, Bhattad DM, Chandak KK, Taksande JB, Umekar MJ. A Review: Pharmacological and herbal remedies in The Management of Neurodegenerative disorder (Alzheimer's). Int J Pharmacogn Life Sci. 2021;2(1):18-27.

7. Pradeep S, Jain AS, Dharmashekara C, Prasad SK, Kollur SP, Syed A, Shivamallu C. Alzheimer's Disease and Herbal Combination Therapy: A Comprehensive Review. J Alzheimers Dis Rep. 2020;4(1):417-29.
8. Obulesu M, Rao DM. Effect of plant extracts on Alzheimer's disease: An insight into therapeutic avenues. J Neurosci Rural Pract. 2011;2(01):56-61.
9. Gao J, Inagaki Y, Li X, Kokudo N, Tang W. Research progress on natural products from traditional Chinese medicine in treatment of Alzheimer's disease. Drug Discov Ther. 2013;7(2):46-57.
10. Lee J, Jin C, Cho SY, Park SU, Jung WS, Moon SK, Park JM, Ko CN, Cho KH, Kwon S. Herbal medicine treatment for Alzheimer disease: A protocol for a systematic review and meta-analysis. Medicine. 2020;99(33):e21745.
11. Geun Kim H, Sook Oh M. Herbal medicines for the prevention and treatment of Alzheimer's disease. Curr Pharm Des. 2012;18(1):57-75.
12. Pei H, Ma L, Cao Y, Wang F, Li Z, Liu N, Liu M, Wei Y, Li H. Traditional Chinese medicine for Alzheimer's disease and other cognitive impairment: a review. Am J Chin Med. 2020;48(03):487-511.
13. Shal B, Ding W, Ali H, Kim YS, Khan S. Anti-neuroinflammatory potential of natural products in attenuation of Alzheimer's disease. Front Pharmacol. 2018;9:548.
14. K Ravi S, Narasingappa Ramesh B, Kj S, Poyya J, Karanth J, Raju NG, G Joshi C. Neuroprotective role of herbal alternatives in circumventing Alzheimer's disease through multi-targeting approach-a review. Egypt J Basic Appl Sci. 2022;9(1):91-124.
15. Sun ZK, Yang HQ, Chen SD. Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease. Transl Neurodegener. 2013;2(1):1-7.
16. Singh AK, Gupta A, Mishra AK, Gupta V, Bansal P, Kumar S. Medicinal plant for curing Alzheimer's disease. Int J Pharm Biol Arch. 2010;1(2):108-14.
17. Tian J, Shi J, Zhang X, Wang Y. Herbal therapy: a new pathway for the treatment of Alzheimer's disease. Alzheimers Res Ther. 2010;2(5):1-4.
18. Perry EK, Pickering AT, Wang WW, Houghton P, Perry NS. Medicinal plants and Alzheimer's disease: Integrating ethnobotanical and contemporary scientific evidence. J Altern Compl Med. 1998;4(4):419-28.
19. Solanki I, Parihar P, Parihar MS. Neurodegenerative diseases: from available treatments to prospective herbal therapy. Neurochem Int. 2016;95:100-8.
20. Essa MM, Vijayan RK, Castellano-Gonzalez G, Memon MA, Braidy N, Guillemin GJ. Neuroprotective effect of natural products against Alzheimer's disease. Neurochem Res. 2012;37(9):1829-42.
21. Sreenivasmurthy SG, Liu JY, Song JX, Yang CB, Malampati S, Wang ZY, Huang YY, Li M. Neurogenic traditional Chinese medicine as a promising strategy for the treatment of Alzheimer's disease. Int J Mol Sci. 2017;18(2):272.
22. Patil SV, Patil VK, Patil PA. Review on herbal medicines of alzheimer's disease. Asian J Res Pharm Sci. 2020;10(3):171-7.
23. Cheung TS, Song TH, Ng TB, Wu FH, Lao LX, Tang SC, Ho JC, Zhang KY, Sze SC. Therapeutic effects of herbal chemicals in traditional Chinese medicine on Alzheimer's disease. Curr Med Chem. 2015;22(19):2392-403.
24. Wang ZY, Liu JG, Li H, Yang HM. Pharmacological effects of active components of Chinese herbal medicine in the treatment of Alzheimer's disease: a review. Am J Chin Med. 2016;44(08):1525-41.
25. Kumar A, Singh A, Aggarwal A. Therapeutic potentials of herbal drugs for Alzheimer's disease—An overview. Indian J Exp Biol. 2017;55:63-73.
26. Zhou S, Dong L, He Y, Xiao H. Herbal medicine for Alzheimer's disease: a systematic review and meta-analysis. Am J Chin Med. 2017;45(07):1327-44.
27. Soheili M, Karimian M, Hamidi G, Salami M. Alzheimer's disease treatment: The share of herbal medicines. Iran J Basic Med Sci. 2021;24(2):123-35.
28. Jiang Y, Gao H, Turdu G. Traditional Chinese medicinal herbs as potential AChE inhibitors for anti-Alzheimer's disease: a review. Bioorg Chem. 2017;75:50-61.
29. Mehla J, Gupta P, Pahuja M, Diwan D, Diksha D. Indian medicinal herbs and formulations for alzheimer's disease, from traditional knowledge to scientific assessment. Brain Sci. 2020;10(12):964.
30. Anekonda TS, Reddy PH. Can herbs provide a new generation of drugs for treating Alzheimer's disease?. Brain Res Rev. 2005;50(2):361-76.
31. Man SC, Durairajan SS, Kum WF, Lu JH, Huang JD, Cheng CF, Chung V, Xu M, Li M. Systematic review on the efficacy and safety of herbal medicines for Alzheimer's disease. J Alzheimers Dis. 2008;14(2):209-23.
32. Nishteswar K, Joshi H, Karra RD. Role of indigenous herbs in the management of Alzheimer's disease. Anc Sci Life. 2014;34(1):3-7.
33. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Dement. 2006;21(2):113-8.
34. WuLi W, Harn HJ, Chiou TW, Lin SZ. Chinese herbs and acupuncture to improve cognitive function in Alzheimer's disease. Tzu-Chi Med J. 2021;33(2):122-27.
35. Fu LM, Li JT. A systematic review of single chinese herbs for Alzheimer's disease treatment. Evid Based Compl Altern Med. 2011;2011:640284.
36. Agarwal P, Alok S, Fatima A, Singh PP. Herbal remedies for neurodegenerative disorder (Alzheimer's disease): A Review. Int J Pharm Sci Res. 2013;4(9):3328.
37. Sharma R, Kuca K, Nepovimova E, Kabra A, Rao MM, Prajapati PK. Traditional Ayurvedic and herbal remedies for Alzheimer's disease: from bench to bedside. Exp Rev Neurother. 2019;19(5):359-74.
38. Sivaraman D, Anbu N, Kabilan N, Kumar MP, Shanmugapriya P, Christian GJ. Review on current treatment strategy in Alzheimer's disease and role of herbs in treating neurological disorders. Int J Trans Res Ind Med. 2019;1(1):33-43.
39. Gregory J, Vengalasetti YV, Bredesen DE, Rao RV. Neuroprotective herbs for the management of Alzheimer's disease. Biomolecules. 2021;11(4):543.
40. Wu TY, Chen CP, Jinn TR. Traditional Chinese medicines and Alzheimer's disease. Taiwan J Obstet Gynecol. 2011;50(2):131-5.
41. Howes MJ, Fang R, Houghton PJ. Effect of Chinese herbal medicine on Alzheimer's disease. Int Rev Neurobiol. 2017;135:29-56.
42. Akram M, Nawaz A. Effects of medicinal plants on Alzheimer's disease and memory deficits. Neural Regen Res. 2017;12(4):660-70.
43. Wu JG, Wang YY, Zhang ZL, Yu B. Herbal medicine in the treatment of Alzheimer's disease. Chin J Integr Med. 2015;21(2):102-7.
44. Arai H, Suzuki T, Sasaki H, Hanawa T, Toriizuka K, Yamada H. A new interventional strategy for Alzheimer's disease by Japanese herbal medicine. Jpn J Geriatr. 2000;37(3):212-5.
45. Yang WT, Zheng XW, Chen S, Shan CS, Xu QQ, Zhu JZ, Bao XY, Lin Y, Zheng GQ, Wang Y. Chinese herbal medicine for Alzheimer's disease: clinical evidence and possible mechanism of neurogenesis. Biochem Pharmacol. 2017;141:143-55.
46. Lee J, Kwon S, Jin C, Cho SY, Park SU, Jung WS, Moon SK, Park JM, Ko CN, Cho KH. Traditional East Asian Herbal Medicine Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis. Pharmaceuticals. 2022;15(2):174.
47. Singh AK, Rai SN, Maurya A, Mishra G, Awasthi R, Shakya A, Chellappan DK, Dua K, Vamanu E, Chaudhary SK, Singh MP. Therapeutic potential of phytoconstituents in management of Alzheimer's disease. Evid Based Compl Altern Med. 2021;2021:5578574.
48. Jeon SG, Song EJ, Lee D, Park J, Nam Y, Kim JI, Moon M. Traditional oriental medicines and Alzheimer's disease. Aging Dis. 2019;10(2):307-28.
49. Santos-Neto LL, de Vilhena Toledo MA, Medeiros-Souza P, de Souza GA. The use of herbal medicine in Alzheimer's disease—a systematic review. Evid Based Compl Altern Med. 2006;3(4):441-5.
50. R Howes MJ, J Houghton P. Ethnobotanical treatment strategies against Alzheimer's disease. Curr Alzheimer Res. 2012;9(1):67-85.
51. Kalász H, Ojha S, Tekes K, Szőke É, Mohanraj R, Fahim M, Adeghate E, Adem A. Pharmacognostical sources of popular medicine to treat Alzheimer's disease. Open Med Chem J. 2018;12:23-35.